Psychoradiological patterns of small-world properties and a systematic review of connectome studies of patients with 6 major psychiatric disorders

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Word count for the text: 6315

Word count for the abstract: 277

Abstract

Background: Brain connectome research based on graph theoretical analysis shows that "small-world" topological properties play an important role in the structural and functional alterations observed in patients with psychiatric disorders. However, the reported global topological alterations in small-world properties are controversial, are not consistently conceptualized according to agreed-upon criteria, and are not critically examined for consistent alterations in patients with each major psychiatric disorder. Here, we describe the main patterns of altered small-world properties and then systematically review the evidence for these alterations in the structural and functional connectomes in patients with 6 different major psychiatric disorders.

Methods: Based on a comprehensive PubMed search we selected 40 studies of schizophrenia, 33 studies of depression, 5 studies of attention-deficit/hyperactivity disorder, 5 studies of bipolar disorder, 7 studies of obsessive compulsive disorder and 5 studies of posttraumatic stress disorder using non-invasive neuroimaging data and graph theory approaches.

Results: The following 4 patterns of altered small-world properties are defined from the perspectives of segregation and integration: 'regularization', 'randomization', 'stronger small-worldization' and 'weaker small-worldization.' Although more differences than similarities are noted in patients with these disorders, one prominent trend is the structural regularization versus functional randomization in patients with schizophrenia.

Limitations: Differences in demographic and clinical characteristics, preprocessing steps, and analytical methods can produce contradictory results, increasing the difficulty of integrating results across different studies.

Conclusions: Four patterns of altered small-world properties are proposed. The analysis of altered small-world properties may provide novel insights into the pathophysiological mechanisms underlying psychiatric disorders from a connectomic perspective. In future connectome studies, the global network measures of both segregation and integration should be calculated to fully evaluate altered small-world properties in patients with a particular disease.

1. Introduction

1.1. The need for a systematic approach to examine connectome abnormalities

Recent advances in neuroscience methodology have underpinned a large increase in human brain research studies. In particular, by taking advantage of non-invasive imaging approaches, the developing field of psychoradiology (https://radiopaedia.org/articles/psychoradiology) promises not only insights into abnormal brain function and underlying neuropsychopathologies, but also potential clinical utility in patients with mental illness, from diagnosis to planning and monitoring therapeutic interventions.[1] Psychoradiological studies have revealed abnormal brain networks in patients with several major psychiatric disorders.[2-5]

However, reported neuroimaging studies to date have sometimes neglected the interactions among multiple brain regions. Widespread and subtle pathology across the brain may be only imperfectly detected using a traditional regional or voxel-based analysis.[6] In contrast, a large-scale network analysis enables the assessment of overall connectivity patterns among all regions of the brain. This approach has been stimulated by pioneering studies modeling the brain as a complex network in the so-called 'connectome'.[7] In these terms, the human brain network exhibits topological properties known as 'small-worldness', an optimal balance between the segregation and integration of information processing procedures.[8] We suggest that a clear definition of the main patterns of altered small-world properties might yield new insights into how these processes are perturbed in patients with pathological brain conditions, with potential benefits to diagnosis and therapy.

Graph theory provides a rigorous mathematical framework to analyze the topology of complex networks.[9] Graph theoretical approaches have been widely applied to connectome studies to investigate the topological organization of large-scale functional and structural brain networks in healthy and disease states.[10-13] Brain disorders clearly cause significant alterations in global network topology;[14] however, connectome studies have often reported inconsistent quantitative accounts of these. Occasionally, similar alterations have been described in terms of different patterns of change. For example, two functional connectome studies in patients with schizophrenia reported a decreased clustering coefficient (C_p) and an increased path length (L_p) compared to healthy controls (HC).[15, 16] However, one study interpreted this result as a tendency toward more random organization,[15] whereas the other study described the result as what we will call here ‘weaker small-worldization’, i.e., a change toward less-marked small-world properties.[16] Conversely, different topological alterations may be interpreted as showing the same pattern. For example, two functional studies of patients with schizophrenia reported a tendency toward a more random organization[15, 17]; however, one study observed an increased L_p and decreased C_p,[15] whereas the other study noted a decreased L_p (marginally group difference) and decreased C_p.[17] Definitions of unified criteria for characterizing small-world properties in terms of global topological parameters are urgently needed.

Furthermore, functional and structural networks may show discrepancies in alterations in small-world properties in patients with the same disorder. For example, in patients with schizophrenia, increased C_p and L_p have been reported in the structural connectome,[18] but decreased C_p and L_p in the resting-state functional connectome.[15] Meanwhile, other studies on the structural and functional connectomes have reported consistent alterations in small-world properties, e.g., decreased global efficiency (E_{glob}) and a maintained local efficiency (E_{loc})[19, 20] and increased C_p and

L_p.[18, 21] Clearly, further studies are required to explore whether there are potential common trends in functional and structural networks.

Several reviews have recently summarized findings for both the functional and structural connectomes in patients with psychiatric disorders.[2, 22-25] However, to date, no study has reviewed the clinically altered small-world properties of the human brain connectome from the perspectives of information segregation and integration. In this review, we explore the main patterns of altered small-world properties using a graph theoretical analysis, and then summarize recent findings from studies of patients with several major psychiatric disorders.

First, we introduce the construction of the brain connectome, connectome measures, and network types (for additional details, please refer to the study by Liao et al.[25]).

1.2. Rationale for brain connectome construction

In graph theory, a brain network is defined as a graph G (N, K), with N and K representing the number of nodes and edges, respectively. Modern brain mapping techniques include structural magnetic resonance imaging (MRI), functional MRI (fMRI), electroencephalography (EEG) and magnetic-encephalography (MEG); we did not consider the latter two techniques, in order to reduce the confounding effects of heterogeneous image acquisition techniques.

Brain nodes are often defined based on anatomical landmarks, functional activation,[26-28] and regional connectivity profiles.[29] Anatomical landmarks include the automated anatomical labeling (AAL) atlas, Harvard-Oxford atlas and Desikan-Killiany atlas; the AAL atlas has also been used,[30] but different investigators have used different numbers of regions. Some researchers have used software tools such as FreeSurfer to parcellate the cortex into a given number, x, of nodes. The majority of templates have constructed brain networks with < 1000 nodes.[31] Independent component analysis (ICA) is the most popular of the many data-driven analyses for delineating resting-state brain functional networks. The number of components identified using the ICA approach is typically less than a hundred for a whole-brain analysis.[26] There is no gold standard for node parcellation. Researchers typically choose network nodes based on anatomic templates for convenience. The use of an anatomical atlas is known to introduce potential bias because of its inhomogeneity, and a reasonable approach used in most neuroimaging studies is to employ a single atlas for analysis.[32] A recent functional study investigating the impact of parcellation choice on group differences found that patient-specific global network properties are robustly observed using different parcellation schemes, whereas graph metrics characterizing impairments of individual nodes vary considerably.[33] Overall, the correct definition of nodes in connectome studies is still an open question that needs further technical investigation.

Once the nodes have been determined, the edges are defined. The edges of the brain functional connectome are constructed by calculating the Pearson, partial, or wavelet correlation for every possible pair of regional time series among the nodes. The Pearson correlation measures the interdependence between two time series. However, correlation may result from indirect relationships with common sources. To avoid this problem, in the partial correlation approach the brain activity in one region is correlated with that in another region after the activity in all other regions is regressed out; this attempts to remove the effects of indirect paths[34] and provides a better estimate of the true macroscopic functional connectome.[35] However, this strategy has the opposite problem of losing real connections, which is likely to underestimate topological measures.[36] The best recent evidence is that Pearson correlation is more valid and reliable.[37]

After construction, the edges of the brain structural connectome can be measured in two ways. The first, using structural data directly, is by computing the chosen (partial or Pearson) correlation coefficients of the morphological features of the brain (cortical thickness or gray matter volume) among nodes. A more advanced approach is by reconstructing diffusion MRI-traced white matter (WM) using either deterministic or probabilistic tractography. The tracking procedure used in deterministic tractography terminates when it reaches regions with fiber crossings,[38] and this tends to reduce sensitivity. Probabilistic tractography overcomes this shortcoming, and offers a natural approach to modeling uncertainty by generating multiple curves originating from a seed point,[39] providing a more comprehensive picture of connectivity. The probabilistic algorithm has better test–retest reliability and is more robust than deterministic tractography in areas of high uncertainty (notably fiber crossings).[40, 41] However, the lower computational cost of deterministic tractography makes it more often used in clinical applications. High-field imaging and the application of advanced diffusion reconstruction algorithms offer the potential to characterize more complex fiber patterns when edges are defined.

Once the nodes and edges are defined, a matrix representation is generated where each entry records the edge weight of corresponding node pairs denoted by the row and column index of the matrix. The reconstructed network is classified as the directed or undirected type, depending on whether the edges display directionality. Depending on whether the edges are assigned with different strengths, a binary network is obtained by thresholding the weights of the edges, where the edges are either 1 (connected) or 0 (unconnected); otherwise, the network is a weighted type.

1.3. Brain connectome measures

Once the brain connectome is constructed, the connectome measurement is calculated. In graph theory, a complex network is characterized by two types of measures, integration and segregation, which represent crucial information processing patterns of the brain and ensure efficient global communication and functional specialization.[42]

1.3.1. Integration measures: L_p, λ and E_{glob}

Specifically, topological integration refers to the efficiency of global information communication or the ability to integrate distributed information in the network, which is measured by the parameters L_p, λ and E_{glob}. The characteristic path length L_p is calculated by averaging the minimum number of connections that link any paired nodes in the network.[43] The normalized characteristic path length λ is the normalized L_p, which is calculated for the mean L_p of 100 matched random networks that preserve the same number of nodes and edges as the real network. The global efficiency E_{glob} measures how efficiently information is exchanged at the global level.[44]

1.3.2. Segregation measures: C_p, γ and E_{loc}

In contrast, segregation refers to the ability of densely interconnected groups of brain regions to perform specialized processing procedures and is measured by the parameters C_p, γ and E_{loc}. The network clustering coefficient C_p is calculated by averaging the C_p over all nodes in the network: C_p is equivalent to the fraction of the node's neighbors that are also neighbors of each other.[43] The normalized clustering coefficient γ is the normalized C_p, which is calculated for the mean C_p of 100 matched random networks that preserve the same number of nodes and edges as the real network. Local efficiency, E_{loc}, measures how efficiently information is exchanged at the local level.[44] The level of clustering measured by E_{loc} expresses the level of local connectedness of a network, with high levels of clustering interpreted as high levels of local organization of the network.[22]

1.3.3. Small-world index σ

The small-world index σ is γ / λ, which is > 1 when the small-world fulfills the conditions of γ > 1 and λ ≈ 1.[43] Graph measures are discussed in more detail elsewhere.[42]

1.4. Brain network types: small-world, regular and random networks

Based on the perspectives of segregation and integration, networks are divided into three main types: small-world networks (high C_p and short L_p), regular networks (high C_p and long L_p) and random networks (low C_p and short L_p). A regular network is characterized by a high C_p (the probability that neighboring nodes are also interconnected with other neighboring nodes) and a long L_p (the average distance from one node to any other node in the network, expressed as the number of links that must be traveled). A random network is characterized by a low C_p and a short L_p. A small-world network has a higher C_p than but a similar L_p to a random network, and has both high global and local information transformation capacities and maintains an optimized balance between segregation and integration. Quantitatively, the small-world index σ should be > 1 for small-world networks, as measured by both γ > 1 and λ ≈ 1.

Although connectome studies have confirmed that the brain networks of patients and HCs all exhibit small-world topology (σ > 1 with γ > 1 and λ ≈ 1), significant group differences in global network measures have been reported, implying different types of alterations in small-world properties in patients with different disorders. However, to date, the conceptualization of these altered small-world properties has varied, with no agreed definitive criteria.

1.5. The aims of this review

This review is designed to address the following questions: (1) Can unified criteria be defined for the altered small-world properties? (2) What are the consistently altered small-world properties in patients with specific psychiatric disorders? (3) Are common alterations observed between functional and structural networks? Specifically, we first propose 4 defined patterns of altered small-world properties, and then systematically review published connectome studies to identify the most consistently altered small-world properties in patients with one of 6 specific psychiatric disorders [schizophrenia, depression, ADHD (attention-deficit/hyperactivity disorder), BD (bipolar disorder), OCD (obsessive compulsive disorder), and PTSD (posttraumatic stress disorder)]. Structural and functional studies are treated separately to assess their consistency and evaluate any discrepancies.

2. Methods

2.1. Study selection

An online search of the PubMed database was conducted using the following search terms: [(schizophrenia) or (depression) or (attention-deficit/hyperactivity disorder or ADHD) or (bipolar disorder or BD) or (obsessive compulsive disorder or OCD) or (posttraumatic stress disorder or PTSD)] and (graph analysis or graph theory or small world or connectome). Nine hundred forty-three studies published before December 1, 2016 were screened. The exclusion criteria were 1) studies that did not examine global properties (C_p, γ, E_{loc}, L_p, λ, E_{glob} and σ); 2) studies that did not compare patients with one of the aforementioned psychiatric disorders with HCs; and 3) studies using EEG or MEG.

In addition to this online search, we manually cross-referenced the studies with the bibliographies of recent reviews in the field to ensure that no studies of significance were omitted from the review,[2, 23, 45] after which 1 additional paper was included.[46] Ninety-five papers reporting global properties were finally included in the current review, including 40 studies of schizophrenia, 33 studies of depression, 5 studies of ADHD, 5 studies of BD, 7 studies of OCD and 5 studies of PTSD.

2.2. Patterns of altered small-world properties

Based on the perspectives of segregation (C_p, γ and E_{loc}) and integration (L_p, λ and E_{glob}), we propose 4 patterns of altered small-world properties (**Table 1 and Figure 1**): regularization, in which the network transforms from a small-world network to a relatively regular network; randomization, in which the network transforms from a small-world network to a relatively random network; stronger small-worldization, in which the network transforms from a small-world network to a relatively stronger small-world network; and weaker small-worldization, in which the network transforms from a small-world network to a relatively weaker marked small-world network.

Regularization was defined where at least one altered measurement of segregation (increased C_p, γ or E_{loc}) and/or at least one altered measurement of integration (decreased E_{glob} or increased L_p or λ) were present. Randomization was defined where at least one altered measurement of segregation (decreased C_p, γ or E_{loc}) and/or at least one altered measurement of integration (increased E_{glob} or decreased L_p or λ) were present. Stronger small-worldization was defined where at least one altered measurement of segregation (increased C_p, γ or E_{loc}) and at least one altered measurement of integration (increased E_{glob} or decreased L_p or λ) were present. Weaker small-worldization was defined where at least one altered measurement of segregation (decreased C_p, γ or E_{loc}) and at least one altered measurement of integration (decreased E_{glob} or increased L_p or λ) were present.

3. Results

3.1. Methodological review of connectome studies

Ninety-five papers reporting on the global properties of functional and structural connectomes were included in our systematic review (**Tables 2-4**). Fifty-three papers used AAL, 7 used the Desikan-Killiany atlas, 6 used the Harvard-Oxford atlas, 1 used the Destrieux atlas, 1 used a spatially unbiased infratentorial template, 1 used a voxelwise approach, and 11 used FreeSurfer to parcellate the cortex into diverse numbers of nodes. The brain nodes in 14 papers were defined based on functional activation, 11 of which performed an ICA. The brain nodes in 1 paper were defined based on the regional connectivity profiles.

Twenty-nine, 11, and 6 papers used the Pearson, partial, and wavelet correlations of the regional time series, respectively, to construct the edges of the functional connectome. One paper estimated functional connectivity in the brain using the higher-order statistical dependence. One paper used the IMaGES algorithm to detect functional connections. In 1 paper, functional networks were built using the correlations among ICA time courses of brain nodes. For the edges of structural connectome of morphological features in the brain, 3 and 2 papers, respectively, computed the Pearson and partial correlations of cortical thickness; 3 papers calculated the Pearson correlations of gray matter volume. For the structural connectome reconstructing diffusion MRI data, 30 and 7 papers, respectively, performed deterministic and probabilistic tractography. One paper used the generalized q-sampling imaging (GQI) to construct the edges.[47]

3.2. Global topological alterations in patients with schizophrenia

Forty-seven datasets from 22 functional and 18 structural connectome studies were included, of which the majority (26) used fMRI, followed by 20 studies using diffusion MRI, and 1 study using structural MRI (**Table 2**). Of the functional studies, 2 recruited subgroups of patients, 1 recruited patients with familial and sporadic schizophrenia and analyzed the data with and without global signal regression (GSR),[48] and the other study recruited patients with and without auditory verbal hallucinations (AVH).[16] One study examined global properties during a task and at rest;[15] another study investigated the networks of the left and right hemispheres.[49] One study explored both the structural and functional connectomes.[16]

3.2.1. Functional connectome studies in patients with schizophrenia

Fourteen studies showed a shift toward randomization,[15, 17, 48-57] including 7 reports of decreased segregation, and 7 reports of decreased segregation and increased integration. Specifically, in the study by Ma et al. (2012), patients with schizophrenia showed decreased segregation (decreased C_p) and increased integration (decreased L_p) at rest.[15] Yu et al. (2011) reported decreased segregation (decreased γ) in the right hemisphere task-related network.[49] Zhu et al. (2016) observed decreased segregation (decreased γ and E_{loc}) with GSR, and decreased segregation (decreased γ and E_{loc}) and increased integration (decreased λ) without GSR, in patients with familial schizophrenia, as well as decreased segregation (decreased E_{loc}) in patients with sporadic schizophrenia without GSR.[48]

Seven datasets from 6 studies showed a tendency toward weaker small-worldization with decreased segregation and integration.[15, 16, 49, 58-60] Specifically, patients with schizophrenia showed decreased segregation (decreased C_p) and decreased integration (increased L_p) during the auditory oddball (AOD) task,[15] and decreased segregation (decreased γ) and decreased integration (decreased E_{glob} and increased L_p) in the left hemisphere task-related network.[49] Patients with schizophrenia with and without AVH showed decreased segregation (decreased C_p and E_{loc}) and decreased integration (decreased E_{glob} and increased L_p).[16]

Four studies showed a tendency toward regularization,[20, 21, 61, 62] including 3 reports of both increased segregation and decreased integration, and 1 report of decreased integration. One study showed a tendency toward stronger small-worldization, with increased segregation (increased C_p) and increased integration (increased E_{glob}).[63] Two studies, however, did not report any significant difference in global properties.[48, 64]

3.2.2. Structural connectome studies in patients with schizophrenia

Twelve studies showed a tendency toward regularization,[16, 18, 19, 65-73] including 11 reports of decreased integration and 1 report of both decreased integration and increased segregation. Five studies showed a tendency toward weaker small-worldization, with decreased segregation and integration.[71, 74-77] Specifically, of the 2 datasets in the study by van den Heuvel et al. (2013), one dataset showed a tendency toward regularization with decreased integration (decreased E_{glob}), and the other independent dataset showed a tendency toward weaker small-worldization with decreased segregation (decreased C_p) and decreased integration (decreased E_{glob}) in patients with schizophrenia.[71] One study showed a tendency toward randomization with increased integration.[78] Three studies, however, did not report any significant difference in global properties.[16, 79, 80]

3.2.3. A summary of altered small-world properties in patients with schizophrenia

Eight hundred and eighteen patients with schizophrenia and 791 HCs, along with 28 datasets from 22 functional studies, as well as 945 patients with schizophrenia and 912 HCs, along with 21 datasets from 19 structural studies, were included. In structural MRI studies, the largest proportion (12 of 21 datasets) of altered small-world properties included regularization in 675 of 945 patients, but in fMRI studies, randomization was observed more frequently (14 of 28 datasets, 390 of 818 patients). Most patients with schizophrenia were currently taking medications; only three datasets comprised drug-naïve and medication-washout patients, and in five datasets medication status was not available. For the datasets including currently medicated patients with schizophrenia, the most prominent trend was still structural regularization (10 of 16 datasets) rather than functional randomization (11 of 25 datasets).

3.3. Global topological alterations in patients with depression

Thirty-four datasets from 16 functional and 17 structural connectome studies were included, and the majority (17) used fMRI, followed by 12 DTI studies and 5 structural MRI studies (**Table 3**). One of the fMRI studies recruited patients with late-life depression (LLD) with and without comorbid amnestic mild cognitive impairment (aMCI).[81]

3.3.1. Functional connectome studies in patients with depression

Four studies showed a tendency toward randomization, including 2 reports of increased integration,[13, 82] and 2 reports of decreased segregation.[81, 83] Specifically, one dataset from the study by Li et al. (2015) showed decreased segregation (decreased E_{loc}) in patients with LLD.[81] Five studies showed a tendency toward regularization, including 3 reports of decreased integration characterized by increased L_p[84, 85] or decreased E_{glob} and increased L_p,[86] 1 report of increased segregation (increased E_{loc}),[87] and 1 report of increased segregation (increased E_{loc}) and decreased integration (decreased E_{glob}).[88]

Three studies showed a tendency toward weaker small-worldization with decreased segregation and integration, including decreased C_p with decreased E_{glob} and increased L_p,[89] and decreased E_{loc} with decreased E_{glob} and increased L_p.[81, 90] Four studies, however, reported no significant differences.[46, 91-93] One study showed a decreased σ.[94]

3.3.2. Structural connectome studies in patients with depression

Four studies showed a tendency toward regularization, including 1 report of increased segregation (higher transitivity used as an alternative to C_p),[95] 1 report of decreased integration (decreased E_{glob} and increased L_p),[96] 2 reports of both increased segregation and decreased integration characterized by an increased γ with a decreased E_{glob} and increased λ,[97] and increased C_p and E_{loc} with increased L_p.[47]

Two studies showed a shift toward randomization with decreased segregation characterized by a decreased γ and E_{loc},[98] as well as a decreased C_p.[99] Two studies showed a tendency toward weaker small-worldization with decreased segregation and decreased integration: one study showed a decreased γ and increased λ,[100] and the other study showed a decreased C_p and E_{loc} along with a decreased E_{glob}.[101] One study showed a tendency toward stronger small-worldization with increased segregation (increased E_{loc}) and increased integration (increased E_{glob} and decreased L_p and λ).[102] Eight studies did not report significant differences.[103-110]

3.3.3. A summary of altered small-world properties in patients with depression

In summary, global topology was not significantly altered in 12 reports, followed by 9 studies showing regularization, 6 showing randomization, 5 showing weaker small-worldization, and 1 showing stronger small-worldization. In one study, the global network alterations, which depend on one single measurement, σ (see Discussion), were difficult to classify. In sixteen datasets, patients with depression were currently taking medicine, 14 datasets comprised drug-naïve and medication-washout patients, and medication status was not available in four datasets. No prominent trends in altered small-world properties were observed either in the medicated patients or in the medication-free patients.

3.4. Global topological alterations in patients with ADHD

Only 5 studies, 3 using fMRI and 2 using DTI, were included (**Table 4**).

Of the fMRI studies, one study showed a shift toward regularization by increased segregation (increased E_{loc}) in patients with ADHD.[111] One additional fMRI study reported decreased segregation (decreased E_{loc}) in the visual attention network of children with ADHD during a task, suggesting a shift toward randomization.[112] Another fMRI study reported no significant between-group differences in C_p, γ, L_p, or λ.[113]

The WM networks in boys with ADHD exhibited decreased integration (decreased E_{glob} and increased L_p and λ),[114] showing a shift toward regularization. A WM study in adults with ADHD reported no significant between-group differences in C_p, γ, λ, or E_{glob}.[115]

3.5. Global topological alterations in patients with BD

Only 5 studies, 3 using fMRI and 2 DTI, were included (**Table 4**).

In the fMRI studies, patients with BD type I showed decreased integration (increased L_p) during a task, indicating a shift toward regularization.[84] Two resting-state fMRI studies included patients with BD types I and II, one suggesting a shift toward regularization characterized by increased segregation (increased C_p) and decreased integration (decreased E_{glob}),[116] and the other showing a lack of significant between-group differences in C_p, L_p, E_{loc} or E_{glob}.[92]

Two WM network studies included patients with BD type I; one study showed a shift toward regularization characterized by decreased integration (decreased E_{glob}),[117] and the other study suggested a shift toward weaker small-worldization characterized by decreased segregation (decreased C_p) and decreased integration (decreased E_{glob} and increased L_p).[118]

3.6. Global topological alterations in patients with OCD

Seven studies, including 4 fMRI and 3 structural MRI studies, were included (**Table 4**).

Of the 4 fMRI studies, 1 study found increased segregation (increased γ) of the top-down control network in patients OCD, suggesting a shift toward regularization.[12] Another 2 fMRI studies showed a tendency toward randomization in patients with OCD, one study (focusing on treatment) reported decreased segregation (decreased γ and E_{loc}) at baseline,[119] and the other study reported decreased segregation (decreased γ) and increased integration (decreased λ) in the orbitofrontal-striato-thalamic circuit.[120] Decreased σ has been reported in children with OCD.[121]

Of the 2 WM network studies, one study reported increased segregation (increased γ) and decreased integration (decreased E_{glob} and increased L_p and λ), indicating a tendency toward regularization,[122] while the other study reported no significant differences in λ or γ.[123] One cortical thickness study showed no significant between-group differences in E_{glob} or E_{loc}.[124]

3.7. Global topological alterations in patients PTSD

Only 5 studies, including 2 fMRI and 3 structural MRI studies, were included (**Table 4**).

Of the 2 fMRI studies, one study reported increased segregation (increased C_p and E_{loc}) and increased integration (increased E_{glob} and decreased L_p) in adults with PTSD, showing a shift toward stronger small-worldization,[11] whereas the other study reported increased segregation (increased C_p and E_{loc}) and decreased integration (increased λ) in children with PTSD, suggesting a shift toward regularization.[125]

Of the 2 WM studies, one study reported increased integration (decreased L_p and λ) in adults with PTSD, indicating a shift toward randomization,[126] whereas the other study reported a shift toward weaker small-worldization in children with PTSD characterized by decreased segregation (decreased E_{loc}) and decreased integration (decreased E_{glob} and increased L_p).[127] In an additional structural network study of gray matter, decreased σ was reported in patients with PTSD.[128]

4. Discussion

Our systematic review highlights several important findings in brain connectome research in patients with psychiatric disorders.

4.1. Summary of the approaches and findings

Based on the perspectives of information segregation and integration, we explicitly propose 4 patterns of altered small-world properties: regularization, randomization, stronger small-worldization and weaker small-worldization. According to these criteria, the most prominent trend in the psychiatric studies reviewed here is the regularization of the structural connectome with randomization of the functional connectome in patients with schizophrenia (**Figure 2**). However, no consistent alterations were observed in patients with depression, ADHD, BD, OCD or PTSD.

4.2. Methodology

Brain connectome research based on graph theoretical analysis has proven that 'small-world' topological properties are important in structural and functional alterations in the brains of patients with psychiatric disorders. However, the reported alterations of small-world topological properties in previous connectome studies are controversial and often contradictory (see the Introduction), which may be partially due to the lack of unified criteria for conceptualizing these alterations. Here, we have attempted to address this issue from the perspectives of segregation and integration to classify altered small-world properties into 4 patterns: regularization, randomization, stronger small-worldization and weaker small-worldization. In future studies we recommend comprehensive calculation of the global network measures of segregation (C_p, γ, and E_{loc}) and integration (L_p, λ, and E_{glob}). Additionally, the small-world index σ should be calculated to define the small-world network: σ is calculated as γ / λ, which is > 1 for a small-world organization that only fulfills the conditions of $\gamma > 1$ and $\lambda \approx 1$. An important technical point is that reporting $\sigma > 1$ is not sufficient to prove small-worldness:[94, 121, 128] A regular network with a large γ (e.g., $\gamma = 3$) and a long λ (e.g., $\lambda = 2$) is possible, which together yield $\sigma > 1$.[129] In other words, regular networks may have $\sigma > 1$, and therefore, both $\gamma > 1$ and $\lambda \approx 1$ are required to prove small-worldness.

4.3. Findings from patients with major psychiatric disorders

We systematically reviewed all current reports examining altered small-world properties in both the structural and functional connectomes of patients with one of 6 major psychiatric disorders. The prominent trend is the structural regularization and functional randomization in patients with schizophrenia. In the structural connectome, large proportions of the reported connectomes were constructed using diffusion MRI, and most node and edge definitions used the AAL 90 template and deterministic tractography to construct weighted networks. In contrast, in the functional connectome, obviously consistent definitions for nodes and edges were not used. In addition, neural activity is shaped, but not defined, by the underlying anatomy,[16] as relatively fixed structural organizations produce diverse functional network patterns.[130] Nevertheless, structural connections constrain and shape the diverse patterns of functional connections, while the functional connection patterns reflect the architecture of structural connections.[131]

Patients with depression did not display consistent alterations in small-world properties. A substantial proportion of alterations preserved global organization, rather than the falling into one of the 4 patterns defined here. Where there were significant between-group differences in the global network measures, most studies on the structural connectome in patients with depression seems to indicate a trend toward regularization. Our attempt to identify consistent altered small-world properties might be limited by the heterogeneity of the patient samples (e.g., age of the patients). An exploratory subgroup analysis of patients with MDD revealed that the structural connectome in patients with LLD[95-97, 99, 104, 105] seemed to show a shift toward regularization.[95-97]

To date, there is too little brain connectome research in patients with ADHD, BD, OCD and PTSD for us to infer consistent alterations in small-world properties. In patients with BD type I, the brain networks appear to show a trend toward regularization. Future research is needed to confirm this speculation.

Several potential factors likely contributed to the variable findings. The first is the preprocessing procedure. Global signal regression is controversial, possibly leading to false-positive results:[132, 133] only a few studies stated that they did not regress out the global signal, and in most studies we could not ascertain any information. Another potential influence is the choice of the correlation metric. Most functional connectome studies used Pearson's correlation coefficient to define network edges. According to a reported test-retest analysis, the reliability of global topological properties is modulated by the correlation metrics and the global signal, with the highest reliability observed for Pearson's correlation-based brain networks without global signal removal.[37] The second confounding factor is the brain parcellation schemes. Lord et al. showed that different parcellation schemes for global network properties are comparably consistent.[33] However, they only presented a comparison between two atlases (AAL and Dosenbach) for the graph theoretical analysis, which might generalizability to many other commonly used atlases. Third, we cannot exclude the potential confounding effects of medications, although the trend toward structural regularization rather than functional randomization was still prominent in the datasets comprising medicated patients with schizophrenia. Several studies showed appearance of significant structural and functional alterations in the brain following the administration of anti-psychotics. [3, 134, 135] Fourth, variability may result from the use of different diagnostic categories for patients with the same disorder. A recent study showed a greater stability for some patients with a first psychosis diagnosis, as assigned using ICD-10 criteria rather than DSM-IV criteria.[136] Fifth, subtype heterogeneity may be a potential confounding factor. For example, two schizophrenia studies recruited subgroups of patients: one study recruited patients with familial and sporadic schizophrenia, and the other study recruited patients with and without auditory verbal hallucinations. Two DTI studies recruited patients with the most common paranoid subtype of schizophrenia: one study recruited a population considered a homogeneous genetic subtype of schizophrenia, namely, the 22q11.2 deletion syndrome (22q11.2DS). A detailed description of the subtypes analyzed in the remaining studies was not reported. We performed an exploratory analysis of subtypes of LLD and BD type I, which was provided by the original reports. Despite the significant variability among the different studies, two prominent trends of structural regularization rather than functional randomization emerged in patients with schizophrenia. Future studies will be facilitated by strategies overcoming these issues of methodological boundaries and patient heterogeneity.

Different alterations in the global property measures belonging to the same perspective were identified. For example, in the structural connectome, decreased γ and increased E_{loc}, both of which belong to the segregation perspective, were found in patients with depression.[102] The analysis of γ and E_{loc} revealed seemingly opposite results; γ decreased, whereas E_{loc} increased in this group of patients. Initially, the results appeared to be contradictory. Notably, γ is normalized relative to C_p of the 100 matched random networks that preserve the number of nodes, edges, and degree distribution of the real network. The ambiguity was likely the result of the choice of a null model for normalization, which was similar to the finding of increased γ and decreased C_p in patients with focal epilepsy.[137] The E_{loc} of each node was similar to its C_p. In this circumstance, we believe that the alterations in small-worldness should be evaluated using non-normalized global measurements.

Inconsistent alterations in several original reports were reported compared to the current criteria. A lower σ in the functional networks in the brains of patients with schizophrenia displays a tendency toward randomization during an AOD task.[15] However, according to the current criteria, decreased segregation (decreased C_p) and decreased integration (increased L_p) suggest a shift toward weaker small-worldization. In another AOD study, decreased segregation (decreased γ) in both the left and right hemisphere task-related networks in patients schizophrenia were reported to be similar to randomization.[49] However, according to the current criteria, decreased segregation (decreased γ) and decreased integration (decreased E_{glob} and increased L_p) indicated a trend toward weaker small-worldization in the left hemisphere task-related networks. In the structural connectome of children with PTSD, decreased integration (decreased E_{glob} and increased L_p) suggested a shift toward regularization.[127] However, according to the current criteria, the decreased integration (decreased E_{glob} and increased L_p) and decreased segregation (decreased E_{loc}) showed a shift toward weaker small-worldization. Those inconsistencies might be attributable to the previous unclear definition of the altered small-world properties.

4.4. Limitations of the present study

This study has several limitations. First, we described the patterns of altered small-world properties from the perspectives of segregation and integration. However, 10 reports only investigated 1 perspective, including 9 reports from 8 studies involving only integration[65, 66, 84, 107, 108, 116, 117, 121] and 1 study involving only segregation.[55] Based on the reported findings from those 10 studies, our hypothesis may be not accurate. For example, increased segregation alone without information on integration will appear as regularization, but stronger small-worldization may actually occur. Second, 3 studies[94, 121, 128] only reported changes in σ, which is not sufficient to determine small-worldness alterations. Third, the differences in preprocessing steps, and analytical methods (e.g., parcellation and correlation calculations)[37, 138-140] can produce inconsistent results, and thus the integration of results across different studies is difficult. Fourth, although 3 studies reported altered small-world properties in patients with schizophrenia and LLD,[17, 95, 110] these differences did not reach statistical significance. Fifth, combining evidence from patients with different disease subtypes will increase the variance of the results. However, detailed subtype information was not available for most studies included. Sixth, most studies reported p values for between-group comparisons and did not show the values of the global properties. A better strategy is to report the magnitude of the effects and differences, because the p value may be a biased estimate. We were consequently unable to perform analyses of effect sizes and publication bias.

4.5. Conclusions and future work

In conclusion, we propose 4 patterns of altered small-world properties, namely, regularization, randomization, stronger small-worldization and weaker small-worldization, and use these patterns to summarize the altered small-world properties in patients with one of several major psychiatric disorders. Although more differences than similarities are observed in patients with these disorders, one prominent trend is the prevalent report of regularization of the structural connectome with randomization of the functional connectome in patients with schizophrenia. An analysis of altered small-world properties may provide novel insights into the pathophysiological mechanisms underlying psychiatric disorders from a connectomic perspective. However, several important challenges for future research remain.

First, as described above, mixed results for the brain networks have been reported. The heterogeneity of the patient samples may be a major reason for these discrepancies. Researchers will need to select more homogeneous samples by more detailed consideration of demographic variables. The accumulation of validated evidence from connectome studies will reveal biological markers that indicate specific phenotypes of psychiatric disorders. Second, the combination of multimodal imaging modalities in future studies will provide additional integrative information to map the patterns of the brain connectome. Third, most of these connectome changes were detected based on cross-sectional data and thus may be influenced by inter-subject variability and unbalanced cohort distributions. Investigations of longitudinal networks are needed. Fourth, caution should be exercised in choosing the most reliable methods for analyzing structural and functional connectomes. For resting-state fMRI studies, higher test-retest network reliabilities are obtained using functionally rather than structurally defined nodes, and Pearson rather than partial correlations.[37, 140] Finally, the emergence of novel connectome analytical approaches (e.g., dynamic connectivity) and imaging protocols (e.g., multiband fMRI) should dramatically increase our knowledge of network dysfunction in patients with brain disorders. Additional imaging research on the connectome in patients with the major psychiatric disorders is urgently needed.

Conflicts of interest: All of the authors report no biomedical financial interests or potential conflicts of interest.

Acknowledgements: This study was supported by the National Natural Science Foundation (Grant Nos. 81501452, 81621003, 81761128023, 81220108013, 81227002 and 81030027), the Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT, grant IRT16R52) of China, the Changjiang Scholar Professorship Award (Award No. T2014190) of China, and the CMB Distinguished a Professorship Award (Award No. F510000/ G16916411) administered by the Institute of International Education. D.L. supported by Newton International Fellowship from the Royal Society.

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Figure legends

Figure 1. Representation of four main patterns of altered small-world properties in the brain connectome, ‘regularization’, ‘randomization’, ‘stronger small-worldization’ and ‘weaker small-worldization’, based on the perspectives of segregation and integration. Regularization is defined as increased segregation and/or decreased integration. Randomization is defined as decreased segregation and/or increased integration. Stronger small-worldization is defined as increased segregation and increased integration. Weaker small-worldization is defined as decreased segregation and decreased integration.

Figure 2. Graph showing the number of reports describing either the ‘randomization’, ‘regularization’, ‘weaker small-worldization’, ‘stronger small-worldization’ or ‘no difference’ in functional and structural brain connectomes between patient groups compared with healthy controls. ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; OCD, obsessive compulsive disorder; PTSD, posttraumatic stress disorder; HC, healthy controls.